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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,889	05/15/2006	Ronald Aung-Din	523.1006US	3655

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EXAMINER	
MCMILLIAN, KARA RENITA	

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,889	AUNG-DIN, RONALD	
	Examiner	Art Unit	
	KARA R. MCMILLIAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-67* is/are pending in the application.

4a) Of the above claim(s) *40,42,44,53-55,59-63,66 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41,43,45-52,56-58,64 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-10-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application is a national stage entry of PCT/US04/19816 which claims the benefit of U.S. Provisional Application No. 60/480,089, filed on June 20, 2003, 60/480,088, filed on June 20, 2003 and 60/513,082 filed October 21, 2003.

Response to Amendment

Applicant's amendments filed March 1, 2010, canceling claims 1-37, amending claim 38 and adding new claims 45-67 have been entered. Claims 38-67 are currently pending.

Election/Restrictions

Applicant's election without traverse of Group III (claims 38-44) drawn to a method of treating migraines, etc. in the reply filed on March 1, 2010 is acknowledged. Applicant's election without traverse of a skeletal muscle relaxant as the species of an active ingredient, sumatriptan as the species of a serotonin agonist, an analgesic as the species of an additional active agent, migraines as the species of a condition, and tizanidine as the species of a skeletal muscle relaxant in the reply filed on March 1, 2010 is also acknowledged.

Claims 40, 42, 44, 53-55, 59-63, 66 and 67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 38, 39, 41, 43, 45-52, 56-58, 64 and 65 are being examined as they read on the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 39, 41, 43, 45-52, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating migraines comprising the administration of a topical formulation comprising tizanidine and/or sumatriptan, does not reasonably provide enablement for a method of treating migraines comprising the administration of a topical formulation comprising any skeletal muscle relaxant and/or any ergot alkaloid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not provide sufficient information to show that a topical formulation containing any skeletal muscle relaxant and/or any ergot alkaloid can be used to treat migraines.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Enablement is

considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the relative skill of those in the art, and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The recited claims of the instant application are drawn to a method for the treatment of migraines comprising administering a topical formulation comprising any skeletal muscle relaxant and/or any ergot alkaloid.

Breadth of the claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The rejected claims are extremely broad. Applicants claim that a topical formulation comprising any skeletal muscle relaxant and/or any ergot alkaloid can be used to treat migraines.

Guidance of the Specification/Working Examples: Applicants have only provided data showing that a topical formulation comprising tizanidine and/or sumatriptan is useful in the treatment of migraines. In addition, Applicants disclose that other similar skeletal muscle relaxants such as those claimed in claim 56 of the instant application and other similar ergot alkaloids, such as those listed in claim 53 of the instant application have a reasonable expectation of similar success.

State of the Art: At the time of the instant invention it was known that certain topical formulations of sumatriptan (an ergot alkaloid) was useful in the treatment of migraines (Peyman U.S. Patent No. 5,855,907-Provided on IDS). At the time of the

instant invention certain skeletal muscle relaxants such as tizanidine was known to be useful in the treatment of migraines (Saper, 2002, Headache, Volume 42, pages 470-482).

Predictability/Unpredictability in the Art: There is a general lack of predictability in the pharmaceutical art. In re Fisher, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). It would be unpredictable for the skilled artisan to treat migraines with a topical formulation containing any skeletal muscle relaxant and/or any ergot alkaloid since the structures of each drug will vary and not all drugs are capable of being absorbed through the skin. Thus it would not be reasonable to expect that any skeletal muscle relaxant and/or any ergot alkaloid would be able to be formulated for topical use. Furthermore since each drug is different the efficacy, potency, and thus the dosages of the different types would vary widely especially for formulations intended for topical use.

The Quantitation of Experimentation Required: In order to practice Applicants invention, it would be necessary for one to conduct an exhaustive amount of experiments. Applicant would need to provide reasonable data showing that any topical formulation containing any skeletal muscle relaxant and/or any ergot alkaloid can be formulated for topical use and also remain efficacious in the treatment of migraines. In order to determine the appropriate use of all topical formulations containing any skeletal muscle relaxant and/or any ergot alkaloid, Applicant would need to perform pharmacokinetic and pharmacological experiments to determine efficacy, potency, etc.

for each of the drugs. Therefore, in order to practice the claimed invention, the amount of experimentation required would be considered undue and burdensome.

In conclusion, Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable." A method for treating migraines comprising the administration of a topical formulation comprising any skeletal muscle relaxant and/or any ergot alkaloid is not enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 recites the limitations active metabolites thereof and prodrugs thereof. However Applicants do not define in the instant specification what these metabolites and prodrugs are. Therefore, it is unclear what the meaning of these terms are.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 39, 41, 43, 45-52, 56-58, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Aung-Din U.S. Publication No. 2003/0013753 A1.

The recited claims of the instant application claim a method of treating migraines comprising applying a topical formulation comprising a unit dose of the skeletal muscle relaxant, tizanidine incorporated into an immediate release excipient on to the skin at the posterior cervical area in close proximity to the brain stem wherein a therapeutic effect is within about 2 hours after topical administration.

Franz et al. teach topical pharmaceutical compositions, comprising a pharmacologically active agent, a water-immiscible organic solvent, an emulsifier, a co-emulsifier and water (page 2 lines 45-58). Franz et al. teach that preferable examples of active agents include especially tizanidine (page 4 lines 26-35). Franz et al. specifically disclose microemulsion composition containing tizanidine (page 4 line 65-page 5 line 17). Franz et al. further teach that in particular, they have surprisingly found that topical administration of tizanidine is feasible and accordingly teach topical pharmaceutical compositions containing tizanidine as an active agent and a method of

topically administering tizanidine to a subject in need of such treatment (page 7 lines 23-28).

Franz et al. teach that in the case of tizanidine a suitable single dose is from 10 to 50 mg and this may last for up to 3 days (page 7 lines 45-46). Franz et al. teach that the microemulsions of the invention may be used for the same indication that other forms of the pharmaceutically active agents are used for, e.g. tizanidine as a myotonolytic (page 7 lines 46-49). Franz et al. disclose an example of a tizanidine microgel which contains water on page 8 lines 18-30. Claims 48-51 of Franz et al. specifically claim topical formulations comprising tizanidine and methods of administering said composition topically.

Franz et al. do not specifically teach treatment of migraines and the hydrochloride salt of tizanidine. Franz et al. do not teach applying the formulation at the posterior cervical area in close proximity to the brain stem. Franz et al. do not teach the combination with sumatriptan. Franz et al. do not teach the specific dosages of tizanidine.

Although Franz et al. do not specifically teach treatment of migraines, Franz et al. teach that the microemulsions of the invention may be used for the same indication that other forms of the pharmaceutically active agents are used for, e.g. tizanidine as a myotonolytic (page 7 lines 46-49).

Saper et al. that tizanidine was shown to be superior to placebo in reducing the overall headache index, as well as mean headache days per week, severe headache days per week, average headache intensity, peak headache intensity and mean

headache duration and thus supports the use of tizanidine in the treatment of chronic daily headache, including migraine, migrainous headache, and tension-type headache (abstract). Saper et al. teach the hydrochloride salt of tizanidine which is the standard formulation, is commercially available as tablets for the treatment of migraines (page 471).

Accordingly, it would be obvious to a person of ordinary skill in the art to use the topical formulation of Franz et al. in the treatment of migraines since Franz et al. teach that said topical formulation can be used for the same indication as other forms of the active agent are used for. Thus, since Saper et al. teach that tizanidine in the tablet form is useful for the treatment of migraines, it would be obvious to a person of ordinary skill in the art that the topical formulation would also be useful in the treatment of migraines. Therefore based on the combination of references, an ordinary skilled artisan would be motivated to use the topical tizanidine formulation of Franz et al. for the treatment of migraines with a reasonable expectation of success. Furthermore, since tizanidine hydrochloride is a standard formulation of tizanidine and the hydrochloride salt would not be expected to alter the physical properties of the active agent, the hydrochloride salt of tizanidine is rendered obvious.

Although Franz et al. do not teach the specific dosages of the topical formulation, it is obvious to vary and/or optimize the amounts of ingredients such that the desired outcome is achieved. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980). Furthermore, it is

obvious to vary and/or optimize the amount of a compound provided in the composition, in order to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Aung-Din teaches formulation and methods of treating a migraine with a serotonin agonist (abstract). Aung-Din further teach a topical formulation comprising the serotonin agonist wherein the agonist is preferably applied to the posterior cervical region of the human experiencing a migraine [0016]. Aung-Din teaches that most, preferably the topical formulation is applied to the back of the neck, preferably in close proximity to or on the area of skin above the brain stem [0016]. Aung-Din further teaches that symptoms of the migraine are relieved within about 2 hours [0017]. Aung-Din further teaches that the preferable serotonin agonist for use in the invention includes sumatriptan [0046]. Aung-Din et al. further teach that the topical formulation comprising the serotonin agonist can include the addition of another active ingredient [0089].

Accordingly, one of ordinary skill in the art at the time of the instant invention would have found it obvious to combine the teachings of Franz et al., which renders obvious a topical composition comprising tizanidine for the treatment of migraines, with the teachings of Aung-Din, which teach that a topical composition comprising sumatriptan is also useful for the treatment of migraines. Thus, since both topical

formulations of tizanidine and sumatriptan are useful for the treatment of migraines, one of ordinary skill in the art would be motivated to combine said ingredients with a reasonable expectation of providing an improved treatment of migraines. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Furthermore, since the topical combination of sumatriptan and tizanidine is rendered obvious for the treatment of migraines, it would also be obvious to apply the composition at the posterior cervical area in close proximity to the brain stem since Aung-Din specifically teach said application for the treatment of migraines. Furthermore since the composition of Aung-Ding provides relief within about 2 hours, it would be obvious that the combination of sumatriptan and tizanidine would also provide relief within about 2 hours.

Regarding claims 51 and 52 of the instant application, since the composition for the treatment of migraines is rendered obvious, the properties of the composition are also rendered obvious since a compound and its properties are inseparable. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Therefore in view of the recited prior art references, claims 38, 39, 41, 43, 45-52, 56-58, 64 and 65 of the instant application are rendered obvious.

Conclusions

Claims 38, 39, 41, 43, 45-52, 56-58, 64 and 65 are rejected. Claims 40, 42, 44, 53-55, 59-63, 66 and 67 are withdrawn. Claims 1-37 are cancelled. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARA R. MCMILLIAN whose telephone number is (571)270-5236. The examiner can normally be reached on Monday-Thursday from 8:30 am- 6:00 pm and every other Friday from 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kara R. McMillian/

Examiner, Art Unit 1627

KRM

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627